Composite Intestinal Adenoma-Microcarcinoid

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▼ Abstract
Composite intestinal adenoma and microcarcinoid is a rare intestinal neoplasm consisting of intermingled adenomatous and well-differentiated neuroendocrine components. A few case reports and small series have suggested an indolent clinical course for this entity. We reported 7 cases of composite intestinal adenoma-microcarcinoid, including their morphologic features and clinical follow-up, both in biopsy and resection specimens. We identified 7 cases of composite intestinal adenoma-microcarcinoid from our pathology database. Five were from the large intestine, and 2 were in the duodenum. Morphologically, all microcarcinoids exhibited low-grade cytologic atypia and were devoid of significant pleomorphism, necrosis, and mitotic activity. Among the 7 lesions, 6 had a lobular architecture with smooth borders and mucosa-confined microcarcinoids; none had neuroendocrine carcinoma in subsequent resections. However, 1 colonic case had carcinoid cells penetrating the muscularis mucosae into the submucosa with an infiltrative border, and the resection showed metastatic high-grade neuroendocrine carcinoma in 1 lymph node. Composite intestinal adenoma-microcarcinoid is extremely rare. Although composite mucosa-confined adenoma-microcarcinoid is likely to have an indolent behavior, submucosal invasion by the neuroendocrine component may be associated with aggressive behavior.

Although subtle neuroendocrine differentiation as detected histochemically or immunohistochemically is a common finding in intestinal adenoma or adenocarcinoma, colorectal tumors containing a significant portion of morphologically recognizable neuroendocrine cells, either diffusely (combined tumors) or locally (composite tumors), that is, mixed glandular-neuroendocrine neoplasms, are uncommon. When both glandular and neuroendocrine components of a lesion have benign histology, it is referred to as “composite adenoma-carcinoid,” and when the carcinoid component is minute or microscopic it is referred to as “composite adenoma-microcarcinoid.” The natural history of intestinal adenoma-microcarcinoid remains largely unknown because of the rarity of this entity. The few case reports and small series to this point have suggested no aggressive behavior of this rare tumor. In this study, we present 7 cases of adenomatous polyps containing a portion of morphologically recognizable neuroendocrine cells.
MATERIALS AND METHODS

Patients

Seven cases of composite intestinal adenoma-microcarcinoid were retrospectively identified from the surgical pathology and consultation files of the Cleveland Clinic. The slides were stained with hematoxylin and eosin, and 4 cases had immunohistochemical stains for neuroendocrine markers (chromogranin A, synaptophysin, and/or CD56). All cases were reviewed by 2 gastrointestinal pathologists (J.L. and X.L.).

Immunohistochemistry

Sections of 4 µm thickness were cut from formalin-fixed paraffin-embedded blocks, deparaffinized, and used for immunohistochemistry. Immunohistochemical staining was carried out with mouse monoclonal anti-chromogranin A (DAKO; 1:100 dilution), mouse monoclonal anti-synaptophysin (BioGenex; 1:1 dilution), and mouse monoclonal anti-CD56 (Novocastra; 1:200 dilution) after routine microwave antigen retrieval.

RESULTS

Case History

Pathologic diagnoses, demographic and patient follow-up data have been summarized in Table 1. The polyps were removed by polypectomy during colonoscopies conducted in 6 patients and by hemicolecction in 1 patient, including 2 women and 5 men, aged 51 to 72 years (mean age, 62 y). In the 6 polypectomies, 4 polyps were found during routine screening colonoscopies; 1 polyp (case 3) was found and removed during follow-up colonoscopy after hemicolecction for a colonic adenocarcinoma at a different site; 1 polyp (case 7) was removed from the sigmoid colon when the patient underwent transanal excision of a synchronous rectal adenocarcinoma in the rectum. None of the patients had any known history of inflammatory bowel disease. The size of the polyps ranged from 5 to 55 mm (mean size, 21 mm; Table 1). Five polyps were found in the colorectum (1 cecum, 1 right colon, 1 sigmoid colon, and 2 rectum), and 2 were found in the duodenum (cases 4 and 5). The cases were followed up for a period ranging from 2 to 32 months, with an average of 13.6 months. Five patients underwent surgical resection [n=4, right hemicolecction (n=2) and proctosigmoidectomy (n=2)] or transanal excision (n=1).

Five cases (cases 1, 4, 5, 6, and 7) were initially diagnosed as composite adenoma-microcarcinoid. Among these cases, 2 patients (cases 1 and 6) whose polypectomies were incomplete underwent proctosigmoidectomy and hemicolecction, respectively; only residual composite adenoma-microcarcinoid was identified. One patient (case 7) had synchronous adenocarcinoma of the rectum and residual adenoma-microcarcinoid in the polypectomy site located in the sigmoid colon in follow-up surgical resection. Two patients (cases 4 and 5) who had composite duodenal adenoma-microcarcinoid, which were believed to have been completely removed by polypectomy, had no follow-up treatment.

Patient 2 underwent right hemicolecction because of the large size of the polyp in the right colon. The polyp contained a composite adenoma-microcarcinoid, which was composed of cytologically low-grade glandular and neuroendocrine cells. One of the lymph nodes showed metastatic high-grade neuroendocrine carcinoma, without an adenocarcinomatous component. No adenocarcinoma or neuroendocrine carcinoma was noted in the resected specimen, except for the involved node. This was a consult case and was diagnosed as “well-differentiated mixed glandular and neuroendocrine carcinoma.” This patient had no known history of a neuroendocrine tumor.

Case 3 had a previous history of colonic adenocarcinoma that had been resected by right hemicolecction, and a composite rectal adenoma-microcarcinoid was found 1 year later during the follow-up endoscopy. This rectal polyp had been initially misinterpreted as adenocarcinoma, and the patient underwent proctosigmoidectomy. However, the proctosigmoidectomy specimen showed only adenoma and microcarcinoid but no evidence of adenocarcinoma or neuroendocrine carcinoma.
Histologic Features

The histologic features of these 7 composite intestinal adenoma-microcarcinoids have been summarized in Table 2. All polyps had a polypoid configuration and were composed predominantly of conventional adenoma. Five were tubular, and 2 were tubulovillous. Two cases had low-grade adenomatous components, and 5 cases had high-grade dysplasia. In all cases, the microcarcinoids represented only a small portion of the polyps. The microcarcinoids were situated in the basal portion of the lamina propria in 6 cases, but in 1 case the microcarcinoid cells breached the muscularis mucosae and superficially invaded the submucosa (case 2). In all cases, the neuroendocrine cells intimately intermingled with the adenomatous component and merged together; hence, in some areas it was difficult to distinguish one from another. The microcarcinoid cells were arranged in clusters, nests, tubules, cords, or were dispersed individually (Fig. 1A, Table 2). Drop-off of neuroendocrine cells from the base of the adenomatous glands was noted in all cases, wherein the surrounding lamina propria contained pale and slightly edematous stromal cells with prominent eosinophils and some lymphocytes, mimicking desmoplasia (Fig. 1B, Table 2).

However, the adenoma-microcarcinoid within this region still demonstrated a lobular architecture, which was more evident at low magnification (Fig. 1A). In some areas, prolapse-type changes were noted, in which the clusters of microcarcinoid cells were completely surrounded by lamina propria with fibromuscular proliferation. Cytologically, the microcarcinoid cells were bland, small, and uniform with a moderate amount of eosinophilic, granular, or pale cytoplasm. The nuclei were relatively uniform, round, centrally located, and contained finely stippled chromatin with inconspicuous nucleoli. Mitotic figures or necroses were not observed in any of the microcarcinoids.

Immunohistochemical stains were available in 4 cases (Table 2). All 4 microcarcinoids were immunoreactive for synaptophysin, and 3 were reactive for chromogranin A. Two cases stained for CD56, and both showed immunoreactivity.

Morphologic Distinction of the Microcarcinoids With Favorable and Adverse Prognoses

Most of the microcarcinoids had no evidence of malignancy in the follow-up resection specimens, except in 1 case (case 2), which showed a metastatic high-grade neuroendocrine carcinoma in 1 lymph node, despite its low-grade neuroendocrine component in the primary site. Cytologically, all microcarcinoids, including case 2, were of low grade without significant pleomorphism, necrosis, or mitotic activity. However, case 2 showed evidence of neuroendocrine cells, which penetrated the muscularis mucosa with invasion into the superficial submucosa with an irregular and infiltrative pattern (Figs. 1C, D).

DISCUSSION

The immunohistochemical detection of neuroendocrine cells is common in colorectal adenomas and adenocarcinomas, in which it is regarded as part of the spectrum of divergent differentiation.7 Conventional carcinoid tumor with a glandular component has been reported to arise throughout the gastrointestinal tract.2 Molecular studies have suggested that both the glandular and neuroendocrine components originate from a common multipotential stem cell.8

Composite adenoma-microcarcinoid of the intestine is an uncommon tumor when it is defined as adenoma containing a minor portion of morphologically recognizable neuroendocrine components by light microscopy. This entity was initially reported by Moyana and Murphy in 1988,4 and its rarity contributes to diagnostic challenges in making an accurate diagnosis. The bland appearance and intimate intermingling of neuroendocrine cells with the surrounding stroma and adenomatous epithelium often make them less readily recognizable on routine hematoxylin and eosin-stained sections. In contrast, the infiltrating growth pattern (irregular and small nests or single cell permeation), focal "desmoplasia"-like stroma, and basal location of these cells can lead to an overdiagnosis of invasive poorly differentiated adenocarcinoma. Indeed, of our 7 cases, 1 was initially misinterpreted as adenocarcinoma because of the profound budding-off appearance and irregular growth of the neuroendocrine nests at the base of the high-grade dysplastic glandular component. Thus, awareness of this entity and attention to
In this report, 1 colonic microcarcinoid with minimal submucosal invasion seemed to develop metastatic high-grade neuroendocrine carcinoma in 1 lymph node. To our knowledge, this is the first report of a low-grade neuroendocrine component in a composite adenoma-microcarcinoid behaving aggressively and metastasizing into a lymph node with an acquired high-grade morphology. Composite small cell undifferentiated carcinomas in colonic adenomas are well described, and high-grade cytologic atypia at the primary site and the regional and/or hepatic metastases are appreciated. In our case 2, the microcarcinoid was low grade in appearance at the primary site, in stark contrast to the high-grade morphology in nodal metastasis. Therefore, prediction of the clinical behavior of microcarcinoids can be difficult on the basis of morphologic assessment of the primary tumor alone, as all microcarcinoids in our series were cytologically low grade, including that found in case 2. The only distinct feature noted in this latter case was minimal submucosal invasion with an infiltrative growth pattern of the microcarcinoid component. Although submucosal invasion of the microcarcinoid component could be an adverse prognostic feature, this observation needs to be confirmed by other studies.

Because of the rarity of this entity, recommendations for therapy are only anecdotal. Because of the unknown biological behavior of an incidentally detected microcarcinoid component, it seems prudent to remove the lesion completely by polypectomy. If the lesion is confined to the mucosa, additional surgery would certainly not be warranted. However, if the microcarcinoid penetrates the muscularis mucosae with involvement of the submucosa, the aggressive biological behavior of the single case in this series would indicate additional therapy. Further studies through multicenter collaboration with long-term follow-up would improve our knowledge as to the natural history and optimal treatment for composite intestinal adenoma-microcarcinoid.

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Key Words: adenoma; microcarcinoid; carcinoid; composite neuroendocrine tumor; endocrine cell proliferation

IMAGE GALLERY

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Table 1

Table 2

Figure 1

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